Biomarker Informed Management of Indeterminate Pulmonary Nodules with a Combined Clinical, Blood and Imaging-based Biomarker Strategy

Abstract

Background – Patients with indeterminate pulmonary nodules (IPNs) at risk of cancer undergo high rates of invasive, costly, and morbid procedures1. We trained and externally validated a risk prediction model which combined clinical, blood, and imaging biomarkers to improve the noninvasive management of IPNs. Methods – In this prospectively collected, retrospective blinded evaluation (PRoBE) study, probability of cancer was calculated for 457 patient-IPN pairs using the Mayo Clinic Model and patients were categorized into low, intermediate, and high-risk groups. A combined biomarker model (CBM) including clinical variables, serum high sensitivity CYFRA 21-1 level, and a radiomic signature, was trained in cohort 1 (n = 171) and validated in cohorts 2-4 (total n = 286). The four cohorts were pooled to recalibrate the model for future clinical implementation. The clinical utility of the CBM compared to current clinical care was evaluated in 2 cohorts.

Findings – The CBM provided improved diagnostic accuracy over the Mayo Clinic AUC of 0.86 vs 0.74. Applying 10% and 70% risk thresholds resulted in a bias-corrected clinical reclassification index for cases and controls of 5.9 and 3.3, respectively. A clinical utility analysis of patient medical records estimated that a CBM-guided strategy would have reduced 32% (CI 25-37%) of all unnecessary procedures while shortening the time-to-diagnosis of cancer from 60 to 21 days in intermediate-risk cancers.

Interpretation – Integration of clinical, blood, and image biomarkers improves noninvasive diagnosis of patients with IPNs, potentially reducing the rate of unnecessary invasive procedures while shortening the time-to-diagnosis.

Blood Biomarker Quantification

The High-Sensitivity CYFRA 21-1 assay measures the difference in response between sample (serum incubated with probe antibody) and reference (serum incubated with control). Comparison of the binding and reference samples enables quantification of the target analyte in complex matrices.2

Conclusions

• This study combines clinical, blood, and imaging biomarkers to produce a risk model for the stratification of patients with IPNs.
• This risk model demonstrates good calibration, provides improved predictive accuracy compared to the clinical standard, and with the results validated in three external cohorts.
• An evaluation of the clinical management of intermediate risk nodules suggests the potential for improvement in clinical utility using a CBM approach.
• Future work will evaluate the clinical utility of CBM in the context of a randomized prospective trial of biomarker-informed management of indeterminate pulmonary nodules.

References


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